

Comments of Sanford H. Barsky, MD, Professor of Pathology, University of California, Los Angeles (on behalf of R.J. Reynolds Tobacco Company).

Introductory Remarks

I would like to respond to your invitation for written comments concerning your recent report, "Proposed Identification of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant, November 2003. I specifically would like to comment on the section that deals with the risk assessment of ETS and breast cancer.

I am a Professor of Pathology at UCLA, a breast cancer researcher and practicing breast pathologist and I am very much interested in studying the etiologies of human breast cancer and defining the molecular mechanisms behind this very important disease of women.

The current draft of the present report of the Air Resources Board starts out by saying that the evidence linking ETS and breast cancer has considerably strengthened since the 1997 Report was published. The 1997 Report entitled, "Health Effects of Exposure to Environmental Tobacco Smoke", considered the relationship of ETS with breast cancer inconclusive and made the statement that this relationship must be interpreted cautiously (1). The current draft of the present report states, "In comparison to studies reviewed in the previous OEHHA report (Cal/EPA, 1997) current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk.... Overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer...."(2).

Comment 1:

Biomarker Studies.

Let's begin with the biomarker studies. The biomarker studies consist of the demonstration that polycyclic aromatic hydrocarbons (PAH) were found in breast tissue of subjects and higher levels were found in their tumors. The levels of PAH adducts were not observed however to be associated with current active or passive smoking exposure. If one examines all the tissues of the body, the highest levels of PAH-adducts are actually found in heart tissue (3), a tissue that does not give rise to cancer and a tissue that is therefore resistant to the effects of smoking-related carcinogens. So the absolute or relative levels of PAH adducts in of themselves do not constitute a meaningful biomarker. If evidence of molecular damage from the adducts such as mutations could be shown in breast tissue such as the characteristic G-T transversion of PAH or if, phenomenon related to genomic instability, such as loss of heterozygosity (LOH) or microsatellite instability as has been shown to be present in bronchial tissues of smokers (4,5) had been demonstrated in breast tumors of people exposed to ETS that in fact would

be evidence of a biomarker. PAH-adducts alone for the reasons cited are not enough. Therefore the weight of biomarker evidence does not support a causal association between ETS and human breast cancer.

Response:

Contrary to the assertion in the comment, several studies have shown that levels of PAH or related aromatic adducts are associated with current and former active or passive smoking exposure. For instance, Firozi et al (2002) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted. [Firozi PF, Bondy ML, Sahin AA, Chang P, Lukmanji F, Singletary ES, Hassan MM, Li D (2002). Aromatic DNA adducts and polymorphisms of CYP1A1, NAT2, and GSTM1 in breast cancer. Carcinogenesis 23(2):301-6.]

Similarly, Faraglia et al. (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend ($P = 0.04$) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status ($P = 0.03$). An increase in adduct levels with passive smoking status alone (never, former, current) was seen but the trend was not statistically significant: a significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking. [Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003). Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke. Carcinogenesis 24(4):719-25.]

The intent of OEHHA's discussions in the document was to point out:

1. *PAHs are found to cause DNA adducts in various tissues.*
2. *Appearance of these adducts correlates with the appearance of tumors at substantial (and therefore easily observable) rates in some tissues.*
3. *Appearance, both of adducts and consequential genetic modifications, correlates with tumor appearance in some tissues.*
4. *Several of these end-points have been demonstrated in breast tissue (in animals or humans) under a variety of circumstances where exposure to PAHs occurred, either as a consequence of exposure to ETS or from some other source. The original report cites various authorities (Li et al. 1999 #1022; Perera et al., 1995; Conway et al., 2002; Santella et al., 2000; Rundle et al., 2000; Li et al., 2002). In addition, the finding by Gammon et al. (2002) of an association between PAH adducts, in mononuclear cells from blood samples, and breast cancer should be considered.*

Given these consistent observations, it is reasonable to describe biomarker evidence as supportive of a causal association between ETS and human breast cancer. Neither OEHHA, nor laboratory research scientists active in this field, have sought to establish that there is a quantitative relationship between the different measures of exposure and effect across different tissues, nor would such a relationship be expected given the different metabolic capabilities, susceptibility to mutation and tumorigenesis, and DNA repair capacities of the many different tissues in the body. Breast tissue is clearly a tissue susceptible to cancer; heart tissue is clearly not. Thus, the argument that the absence of heart cancer in the presence of measurable DNA adducts in heart tissue implies no connection between DNA adducts and cancer in general is invalid. OEHHA is not asserting that the biomarker evidence is sufficient in isolation to establish the causal association between ETS and human breast cancer, but rather that it contributes substantially to the overall weight of evidence in favor of such a conclusion (which is based primarily on epidemiological findings).

Comment 2:

Animal models of breast cancer

Animal models purporting an association of ETS and breast cancer are also lacking. Most animal models of breast cancer are mouse models and are related to either the mouse mammary tumor virus (MMTV) or the genetically engineered mouse (GEM) where certain oncogenes such as myc and neu are overexpressed (6). There are only a few models of PAH induced mammary tumors, the most common example of which is dimethylbenzanthracene (DMBA). However carcinogen-induced mammary tumors including DMBA are not metastatic (6). Hence the scarcity and overall relevance of these murine models to ETS and human breast cancer is questionable. Certainly the weight of the evidence provided by these animal studies is not sufficient to show a causal association between ETS in breast cancer.

Response:

The study cited in the comment is the title (but not session titles or abstract numbers) of a recent symposium at which only a small part of the overall issue of animal models of mammary cancer was addressed. In particular, although some mouse strains (including many C3H and DBA mice) obtain their sensitivity to mammary carcinogens on a latent infection by a mouse mammary tumor virus (MuMTV), other strains, including the B6C3F1 hybrid used as the standard test strain by NTP, do not show the characteristic histological signs of MuMTV infection (Seely JC and Boorman GA 1999. Chapter 23 in Pathology of the Mouse, Maronpot R, Editor, Cache River Press, Vienna, IL). Many chemically induced tumors are classified histologically as carcinomas, and invasion and metastasis are observed (idem). The statement on the “common example ... dimethylbenzanthracene (DMBA) ... relevance of these murine models is questionable” (emphasis added) appears not to give sufficient consideration to the fact that the usual mammary tumor model with 7,12-DMBA uses the female Sprague-Dawley rat, not the mouse. Contrary to the implication in the comment, the tumors formed in this model are considered to include carcinomas, which by definition are metastatic. Although investigators have shown the involvement of tumor viruses in some models of mammary carcinogenesis in both the rat and the mouse, this is not universal. The comment also appears to discount the possibility that chemical/virus interactions could be relevant to human disease. This is unjustified, since our considerable ignorance in this area is

relieved only by a few examples in which such interactions are known to be important (e.g. aflatoxin and Hepatitis B virus which interact in humans to produce liver cancer). With regard to the relevance of animal models to human disease, Thompson and Singh state:

“The sequential steps most commonly described in the natural history of breast cancer are: ductal hyperplasia, atypical ductal hyperplasia, carcinoma in situ, and invasive carcinoma. Evidence will be presented that the development of mammary carcinoma in the rat has a similar natural history.” [Thompson HJ, Singh M (2000). Rat models of premalignant breast disease. J Mammary Gland Biol Neoplasia. 5(4):409-20.]

Evidence of DNA adduct formation, p53 oncogene activation and similar parallel findings in rodent models and in exposed humans was documented in the OEHHHA report.

Comment 3:

Past epidemiological studies really have provided the weight of the evidence suggesting a causal association between ETS and human breast cancer but the current draft of the present report either ignores mentioning or does not give the appropriate weight to recent studies which refute this association. Before I cite and discuss these recent studies, I would like to point out some of the shortcomings of many of the previous studies which the current draft cites.

Firstly, it is important to emphasize that human breast cancer is a heterogeneous disease consisting of both life-threatening variants, breast-threatening variants and innocuous variants which are incidental findings. Obviously the first of these disease types is of more concern to the general public than the last of these types. The vast majority of the epidemiological studies cited in the current draft lumps all of breast cancer together. The few studies which look at breast cancer mortality (the first of these disease types) find no association with ETS.

Response:

Breast cancer types may be divided in regards to their histologic type, encapsulation vs metastatic, receptor presence, etc. Other characteristics such as age at discovery have prognostic value. The assertion above that there is a distinction between breast-threatening and life threatening breast cancer as a distinct disease type is inaccurate. While studies appropriately lump various of these issues together for analysis, the studies that review incident data are, in general, pathologically defined breast cancer that is at

least potentially life threatening. Breast cancer diagnosis is of great importance to both the individuals that receive that diagnosis and to society in general and the financial cost alone makes this disease highly important to the general public. Unfortunately, there is indeed significant mortality among the cases diagnosed as part of the incident breast cancer studies. While there are clearly differences in the aggressivity of breast cancers (with higher aggressivity associated with those more common in premenopausal cancers for which a stronger association with ETS exposure is evident), the commentator presents no evidence that supports the conclusion that there is a distinction, based on disease causation, between fatal and non-fatal breast cancer as defined in epidemiologic studies.

We are unaware of any accepted diagnostic staging scheme that considers any breast cancer whether found incidentally or upon biopsy completely innocuous. The comment probably refers to DCIS or ductal carcinoma in situ, although that is not specified in the comment. This is a cancer that is confined to the milk ducts and not yet invasive. However, DCIS can and does become invasive in some patients with substantial morbidity and mortality. Furthermore, the comment indicates that “breast-threatening variants” of cancer are not concerning to the public. The treatment of so-called “breast-threatening” breast cancer can involve considerable morbidity, including mastectomy, and depending on a number of prognostic indicators, chemotherapy and radiation therapy which often follow even when there is no evidence of metastasis. The psychological consequences of mastectomy in and of themselves can be costly in terms of quality-of-life issues for some women. Thus, there is real reason to take issue with the comment’s classification of “breast-threatening” variants as not concerning to the public. And finally, death from breast cancer can and does occur even with very favorable prognostic indicators, and even in those originally diagnosed with DCIS. Thus, the comment’s contention that some breast cancers are not of concern is invalid.

Also, in this comment it is implied that from an epidemiologic perspective the studies of mortality are actually the most valid and preferred study design. This is not the case. Cancer mortality studies have recognized limitations, particularly those limited to case ascertainment via death certificate. They generally lack information on stage of

diagnosis, duration of illness, treatment or other access related issues that influence cancer survival, particularly in cases diagnosed or reoccurring in periods prior to death (and therefore not likely to be listed as a primary or secondary cause of death). The relationship between disease and exposure, particularly in a chronic disease with good survival (at least at early diagnosis), diminishes over time, and potentially is underestimated in the population under study if surveillance is based on death alone.

Comment 4:

Secondly, it is important to emphasize that the data demonstrating a relationship between ETS and human breast cancer must do so in a biologically plausible manner. If there indeed is an association between ETS and human breast cancer, there must be an association between mainstream smoking and breast cancer and the latter association must be stronger. That is so because the carcinogenic exposure is greater with mainstream smoke. Yet none of the epidemiological studies that the current draft cites show a greater association with mainstream smoking (7-11). An argument advanced to reconcile this disparity is that the control group may have consisted, in part, of people exposed to ETS and thus had a higher rate of breast cancer than would have been expected (2). Differences in breast cancer incidence between this control group and the smoking group would have therefore been minimized. However even this argument would fail to explain why the rate of breast cancer was not higher in the smoking group. The smoking group would consist of subjects exposed to mainstream smoke and hence to the maximal levels of carcinogens. The control group even if it was composed of never smokers and subjects exposed to ETS would still have an overall reduced level of carcinogen exposure and therefore a reduced incidence of breast cancer compared to the mainstream smoking group. But that was not what was observed. Smokers did not have a higher incidence of breast cancer than ETS exposed subjects.

Thirdly, none of the epidemiological studies mentioned in the current draft propose a credible biological mechanism to explain the observations of the study on the relationship of ETS to breast cancer. For example, there is no demonstration that people exposed to ETS have a higher level of cotinine or a higher level of DNA adducts or more mutations in their breast tissue than controls.

Response:

The comment indicates that breast cancer could not possibly be caused by ETS if it is not caused by active smoking. The basis for this contention is that active smokers have higher exposures to carcinogens in cigarette smoke than passive smokers. This would only be true if the concentrations and physical state of all tobacco smoke carcinogens are the same in mainstream and sidestream smoke. This is not the case – some carcinogens

*occur at significantly higher concentrations in side stream smoke due to the different combustion conditions that generate sidestream versus mainstream smoke. In addition, the contention that if active smokers do not have higher rates of breast cancer than passive smokers, ETS could not be a cause of breast cancer in passive smokers also ignores the anti-estrogenic activity of active smoking. Since many breast tumors are estrogen-receptor positive and are dependent upon the presence of estrogen for growth, then anti-estrogenic characteristic of active smoking would actually mitigate effects of carcinogens to some extent. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship (typically, *faute de mieux*), in this case this assumption is neither necessary, nor supported by the data.*

The comment also indicates that the data available on active smoking and breast cancer do not suggest an association. We do not think that is entirely accurate. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of spousal smoking habit as a sole, dichotomous measure of ETS exposure seems inadequate since it largely fails to capture the extent of exposure during the period of greatest sensitivity. There are a number of studies now which note positive associations between active smoking and breast cancer, the recent study (noted by the commentator below) by Reynolds et al. (2004) being an example. This is a prospective cohort study that has been published since the original draft of this document. In this study of California teachers smoking is significantly associated with development of breast cancer and significant trends are noted with increasing duration and intensity of exposure. Details of this study have been added to the revised document.

The comment also minimizes the effect of exposure misclassification on the studies of passive smoking and breast cancer. We do not agree that this effect is minimal. It is difficult to ascertain exposure to ETS over the long-term past. Most studies do a relatively limited assessment of exposure by asking about either spousal exposure or workplace exposure. However, the studies that did a better job of ascertaining exposure in both and had referent groups that had very minimal exposure show statistical correlations between long-term passive smoke exposure and breast cancer.

Finally, we address the last argument in this comment that “there is no demonstration that people exposed to ETS have a higher level of cotinine or a higher level of DNA adducts or more mutations in their breast tissue than controls”. This is in fact incorrect. As discussed in Part A, a large number of studies have demonstrated that ETS exposure is measurable via cotinine levels in the blood (see for example Pirkle et al., 1996). In addition, studies have shown elevated PAH DNA adducts in breast tissue of breast cancer patients relative to controls (Rundle et al., 2000), and higher levels of polycyclic aromatic and 4-aminobiphenyl DNA adducts in breast tissue have been observed in smokers relative to nonsmokers (Li et al., 1996; Firozi et al., 2002; Faraglia et al., 2003; see discussion Section 7.4.1.7 Part B).

Comment 5:

Fourthly, the present draft cites many studies with very small numbers of patients (8,12). When dealing with relative risks or odds ratios in the 1.x range, large numbers of subjects are essential for conclusions of statistical significance.

Fifthly, the present draft cites studies which are mainly retrospective and not prospective in nature (10,11,12). Retrospective studies are inherently much weaker than prospective studies. Only a single prospective study (13) is cited by the present draft. This study by Jee et al. showed an increased incidence of breast cancer in spouses exposed to ETS from their husbands' smoking but whether this association rose to statistical significance can be raised.

Response:

The RR for wives of current smokers for greater than 30 years in Jee et al. was 1.7 (95% CI 1.0-2.8). The number of breast cancer cases (n=138) in this study limits the power to

detect an association and contributes to the relatively large confidence intervals noted. While study sizes vary amongst the studies reviewed, many had sufficient size to identify relative risks of statistical significance and did so. As well, the OEHHA combined studies, using standard methods, in the summary section. Whether analyzing the studies as a whole or the subset of studies with better measures of exposure OEHHA identified statistically significant associations between ETS exposure and breast cancer. Measures were robust to inclusion or exclusion of any individual studies.

Although prospective cohort studies in general have the potential to be preferable for examination of risk, all of the ETS/breast cancer prospective cohort studies suffer from incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Rothman and Greenland (Modern Epidemiology, 2nd edition). A fundamental requirement for study validity is a level of accuracy in exposure ascertainment. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontam et al., a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements.

The comment that only a single prospective study is presented is not correct. In the original draft four ETS/breast cancer cohort studies are reviewed (Egan, Jee, Wartenberg, and Nishino). The discussion of each includes strengths and weaknesses. To these Reynolds et al.(2004) has been added in the revised document.

Comment 6:

Sixthly, some studies cited in the present draft, e.g. Lash et al. (11), published in 1999 and showing an association between ETS and breast cancer were refuted in subsequent studies by the same authors, eg. Lash et al. (14) in 2002.

Seventhly, the studies linking genetic polymorphisms with breast cancer risk and ETS are inconclusive or show no association between ETS and breast cancer irrespective of polymorphisms (15,16).

Response:

Both papers by Lash et al. are reviewed and considered in the document. The 2002 paper was published as a “brief communication” and so details of the study results are limited. As would be expected, there is not 100% concordance of study results evaluating risk of breast cancer and ETS. The preponderance of the evidence from these studies does, however, support the conclusions reached in the document.

Much of the recent relevant work looking at genetic polymorphisms and susceptibility to breast cancer has been done with active smoking. While we agree that any genetic susceptibility modifying the relationship between tobacco smoke and breast cancer has yet to be firmly established, the majority of studies now find either statistically non-significant or significant interactions between human genetic characteristics, smoking, and breast cancer incidence. The level of statistical significance is a function of the size of these studies which have been limited by financial and other considerations. Additionally, accounting for the full spectrum of interactions necessary to fully explore possible risk is difficult as there may be interactions between age at exposure, age at first pregnancy, intensity and duration of exposure, genetic phenotype, etc. A meta-analysis of the various studies is not feasible since there are few studies which have measured outcomes for the same variables. Below is a chart of recent studies exploring genetic polymorphisms and susceptibility to breast cancer among active smokers which we have added to the active smoking section of the document. As noted in the chart, there are some studies which indicate strong effects of metabolic enzyme profiles, although others may not. Looking at a single enzyme does not give the complete picture because there are many different carcinogens in tobacco smoke metabolized by several different enzymes (both Phase I and Phase II). Thus the resulting net effect for a given individual depends on the entirety of the metabolic enzyme profile as far as dose of ultimate carcinogen is concerned. In addition, Couch et al. (2001) found that those smokers with high familial rates of breast and ovarian cancer have high elevated risk of breast cancer compared to nonsmokers. The point we are making is that genetics plays a role in chemical

carcinogenesis and there appears to be susceptible subpopulations for carcinogenicity of tobacco smoke.

Gene Polymorphisms and Genetic Susceptibility to Breast Cancer Among Active Smokers

<i>Study</i>	<i>Polymorphism</i>	<i>Target group</i>	<i>Comparison group</i>	<i>OR (95% CI)</i>
<i>Millikan et al., 1998</i>	<i>NAT2¹ fast</i>	<i>Quit smoke ≤ 3 yr</i>	<i>Never smoker with and without ETS exposure</i>	
		<i>Postmenopausal</i>		<i>7.4 (1.6; 32.6)</i>
	<i>NAT2 slow</i>	<i>Premenopausal</i>	“	<i>1.5 (0.6; 4.0)</i>
		<i>Postmenopausal</i>	“	<i>2.8 (0.4; 8.0)</i>
		<i>Premenopausal</i>	“	<i>1.9 (0.5; 7.9)</i>
		<i>Current smokers</i>	“	
		<i>Postmenopausal</i>	“	<i>1.4 (0.7; 2.8)</i>
		<i>Premenopausal</i>	“	<i>1.1 (0.5; 2.3)</i>
<i>Morabia et al., 2000</i>	<i>NAT2 fast</i>	<i>Postmenopausal</i>	<i>Never-smoker, no ETS</i>	<i>8.2 (1.4; 46.0)</i>
	<i>NAT2 slow</i>	“	<i>ETS only</i>	<i>2.5 (1.0; 6.2)</i>
	<i>Fast & slow</i>	<i>Premenopausal</i>	<i>Never-smoker, no ETS</i>	<i>2.9 (1.1; 7.5)</i>
<i>Delfino et al., 2000</i>	<i>NAT2</i>	<i>Postmenopausal</i>	<i>Low risk controls</i>	<i>1.29 (0.74 ; 2.27)</i>
		<i>Premenopausal</i>		<i>1.15 (0.49 ; 2.79)</i>
		<i>All ages</i>		<i>1.25 (0.27; 5.82)</i>
<i>Krajinovic et al., 2001</i>	<i>NAT2 fast</i>	<i>BC² smokers (pre-& post)</i>	<i>BC nonsmokers</i>	<i>2.6 (1.1; 6.3)</i>
<i>Chang- Claude et al., 2002</i>	<i>NAT2 fast</i>	<i>Pre- and post- menopausal</i>	<i>Never-smoker, no ETS</i>	<i>1.22 (0.59; 2.54)</i>
	<i>NAT2 slow</i>		“	<i>1.67 (0.67; 2.89)</i>
<i>Zheng et al., 2002</i>	<i>GSTT1³ null</i>	<i>Smoke start <18 Postmenopausal</i>	<i>Never-smokers</i>	<i>2.9 (1.0; 8.8)</i>

	<i>GSTT1</i> positive			1.1 (0.6; 1.9)
	<i>GSTT1</i> null	Pre- and post-	Never-smokers	1.7 (0.8; 3.7)
	<i>GSTT1</i> positive	Menopausal		1.0 (0.7; 1.6)
		Current smokers		
	<i>GSTT1</i> ³ null	Postmenopausal	Never-smokers	2.3 (0.6; 8.9)
	<i>GSTT1</i> positive			1.1 (0.6; 2.1)
	<i>GSTT1</i> null	Pre- and post-	Never-smokers	1.1 (0.4; 2.7)
	<i>GSTT1</i> positive	Menopausal		1.1 (0.6; 1.9)
Saintot et al., 2003	Val <i>CYP1B1</i> ⁴	Pre- and post-	Leu/Leu nonexposed	2.32 (1.00; 5.38)
	His <i>SULT1A1</i> ⁵	menopausal	Arg/Arg nonexposed	2.55 (1.21; 5.36)
	Met <i>COMT</i> ⁶		Val/Val nonexposed	1.42 (0.65; 3.13)
Couch et al., 2001	High familial	1 st degree relative	Never-smokers	1.8 (1.2; 2.7)
	BC risk	2 nd degree	“	1.1 (0.8; 1.5)
		Married in	“	1.2 (0.9; 1.6)
	Highest risk (5+ family members affected) ⁷	Sisters and daughters		
		SMR	“	5.8 (1.4-23.9)
				2.3 (0.9-6.0)

¹NAT2 = N-acetyltransferase; ²BC = breast cancer; ³*GSTT1* = Glutathione S transferase T1
⁴*CYP1B1* = Cytochrome P-450 1B1; ⁵*SULT1A1* = Phenol-sulphotransferase 1A1; ⁶Catechol-O-methyltransferase; ⁷Highest risk families were defined two ways: those with five or more members with either ovarian of breast cancer or those with two or more observed cancers than expected. From the latter definition was derived the number based on the SMR.

Comment 7:

Finally and most importantly the present draft fails to cite or properly acknowledge the importance of recently emerging powerful and compelling prospective studies published since 2000 all of which have showed no association between ETS and breast cancer (17-20). These prospective studies have the power of large number of subjects enrolled and have been published in peer reviewed journals of the highest impact factors. In the first study, the Reynolds study (2004) (17), which was just recently published, it was found

that current smoking was associated with increased breast cancer risk relative to all nonsmokers in women without a family history of breast cancer but not among women with such a family history. Furthermore, breast cancer risks among never smokers reporting household passive smoking exposure were not greater than those among never smokers. Their study provided evidence that active smoking but not passive smoking exposure may play a role in breast cancer etiology.

Response:

We agree that the evidence linking active smoking with breast cancer is strengthened by Reynolds et al. (2004). The study as published has the same limitations of the other prospective studies. That is, the exposure assessment for ETS is limited to residential exposure. Important measures of exposure may have been missed by not including work or other exposure history. Indeed, Reynolds notes that “during the 1980s the workplace replaced the home as the primary source of exposure in this cohort” (Reynolds correspondence JNCI 96 (13) 1042-3, 2004).

Comment 8:

In the second study, the Wartenberg study (2000) (18), the authors concluded that, "In contrast to the results of previous studies, this study found no association between exposure to ETS and female breast cancer mortality. The results of our study are particularly compelling because of its prospective design as compared with most earlier studies, the relatively large number of exposed women with breast cancer deaths and the reporting of exposure by the spouse rather than by proxy". The third study, Nishino et al. (19), and the fourth study, Egan et al. (20) are also both prospective studies showing no relationship between ETS and breast cancer.

Because of all these cited reasons, I am concerned that the conclusion of the present draft concerning the relationship between ETS and breast cancer simply is not supported by the data and that the most recent and most powerful studies have not strengthened the association between ETS and breast cancer but actually weakened it. It is important in considering the totality of evidence not simply to add up the studies for and against an observation but to rank order the studies. All studies in science are not created or conducted equally ! For example studies with large numbers, of subjects, all other things being equal, are superior to studies with a small number of subjects. Prospective studies, all other things being equal, are superior to retrospective studies. Studies published in highly regarded peer reviewed journals with high impact factors (the average number of times their articles are quoted by other studies), all other things being equal, are superior to studies published in less known journals with low impact factors. Studies which are peer reviewed are superior to studies which are not peer reviewed such as letters to the editor, etc.

Response:

We have indicated clearly that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure, that these studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer; and that in at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. Although these cohort studies in general have the potential to be preferable for examination of risk, all three of these studies suffer from seriously incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Rothman and Greenland (Modern Epidemiology, 2nd edition) and was addressed in the earlier draft for the first two studies and in the revised draft for the Reynolds paper. A fundamental requirement for study validity is a level of accuracy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all important measures of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontam et al., a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements.

Comment 9:

Simply stated, the studies which show no association of ETS with breast cancer are prospective, comprised of large numbers of subjects, recent and published in journals of the highest impact factors (17-20). The studies which show a relationship of ETS with breast cancer are retrospective, comprised of a small number of subjects, older and published in low impact journals (8,10,12) or published not as peer reviewed articles at all but rather as letters to the editor (21,22).

Response:

The above comment is misleading. While we agree that references 17 through 20 are large prospective studies published in peer reviewed journals the implication that the

studies finding an association with ETS are old, small, and published in “low impact” journals is not correct. First, the papers reviewed in the draft document were published since the previous volume (1997) so none were “old”. We added some further discussion of a few prior studies which had few details in our original volume. As far as the size of the retrospective studies being “small”, examples of study enrollment include; Johnson et al. (2000) with over 2,300 incident primary breast cancer cases, Millikan et al. (1998) had 498 cases and 473 controls, Morabia (1996) had 244 cases and 1,032 controls, and Kropp and Chang-Claude (2002) with 197 cases and 459 controls. The journals in which these were published include Cancer Causes and Control, Cancer Epidemiology Biomarkers and Prevention, American Journal of Epidemiology (Morabia and Kropp and Chang-Claude). These are highly respected and influential journals. The letters to the editor are cited for reference only and do not include primary study data except where corrections have been published.

Comment 10:

It is also pertinent to point out to the Air Resources Board that another environmental protection agency, the International Agency for Research on Cancer, whose overall mission is similar to that of the California Environmental Protection Agency and who, in the past, has warned the public about the risks of smoking and the dangers of ETS issued the following report in 2002: "Concerns that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking is unjustified by the evidence" (23). Their report further goes on to state: "The collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent. Although 4 of the 10 case control studies found statistically significant increased risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal association between involuntary exposure to tobacco smoke and breast cancer in never smokers. The lack of a positive dose response also argues against a causal interpretation of the findings. Finally the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking."

Response:

There are number of reasons why the conclusions of the Cal/EPA report may differ from other evaluations, such as that recently published by IARC. In the case of the association

with breast cancer, we were able to include some studies and meta-analyses, which were unavailable to IARC at the time of their report. OEHHA staff and consultants also undertook different (and more extensive) analyses of data and metadata than those used by IARC.

Comment 11:

Certainly both mainstream smoking and exposure to ETS are not good things for our society to have to deal with and it would be best if these practices could be eliminated. But it is important to accurately evaluate which diseases are and which diseases are not associated with either exposure.

One may ask what is the danger of overstating a potential risk factor in the etiology of any disease. The danger is that it will detract from finding the real culprit. In the case of breast cancer, we really do not know what the cause of the disease is and we need to find out. We need also to identify the major risk factors (both environmental and genetic) to explain sporadic breast cancer, by far the most common type of breast cancer.

Response:

We agree that the conclusion in relation to breast cancer and smoking is extremely important. We consider that the “credibility of the review process” is equally jeopardized by a premature decision in favor of causality and by a failure to respond to new and important findings and analyses that support that conclusion. We have received a number of comments about this conclusion, some supportive and some not. Having carefully reviewed the comments by Dr. Barsky and others we conclude that the existing evidence indicates that the association between ETS exposure and increased incidence of breast cancer may reasonably be considered causal.

Comment 12:

As presently stated, the current working draft of the Air Resources Board claims that overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer. I fear that this current draft has not given enough weight to the newer emerging prospective studies that have been published in outstanding peer review journals of high impact factors that show no association of ETS with breast cancer and has ignored the recent 2002 report of the International Agency for Research on Cancer that also concludes that there is no such association. These studies should be acknowledged and the report's conclusions about the

association of ETS and human breast cancer should at least be modified in the face of this new emerging data.

I would hope that the arguments advanced in this letter would cause the Air Resources Board to at least rethink its position on this matter.

Response:

OEHHA disagrees with the conclusions expressed in this comment, as noted in the earlier detailed responses.

Concluding remarks:

I wish to disclose to the Air Resources Board that I was contacted by R.J Reynolds and asked to review the current draft of the report of Chapter 7, conduct a review of the medical and scientific literature on breast cancer and ETS and prepare my written comments. I was compensated for the time spent on these endeavors.

References cited in comments

1. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Health Effects of Exposure to Environmental Tobacco Smoke, Final Report, September, 1997.
2. California Environmental Protection Agency, Air Resources Board, Office of Environmental Health Hazard Assessment, Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant [Draft], December 2003.
3. Randerath E, Miller RH, Mittai D, Avitts TA, Dunsford HA, Randerath K. Covalent DNA damage in tissues of cigarette smokers as determined by 32P-postlabeling assay. J Natl Cancer Inst 81: 341-347, 1989.
4. Wistuba 11, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, Samet JM, Srivastava S, Minna JD, Gazdar AF. Molecular damage in the bronchial epithelium of current and former smokers. J Natl Cancer Inst 89: 1366-1373, 1997.
5. Mao L, Lee JS, Kurie JM, Fan YH, Lippman SM, Lee JJ, Ro JY, Broxson A, Yu R, Morice RC, Kemp BL, Khuri FR, Walsh GL, Hittelman WN, Hong WK. Clonal genetic alterations in the lungs of current and former smokers. J Natl Cancer Inst 89: 857-862, 1997.
6. Advances in human breast cancer research: Preclinical models. The 24th Congress of the International Association for Breast Cancer Research. Sacramento, CA 2003.
7. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. Am J Epidemiol 156: 616-626, 2002.

8. Morabia A, Bernstein M, Heritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol* 143: 918-928, 1996.
9. Smith SJ, Deacon JM, Chilvers CED. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br J Cancer* 70: 112-119, 1994.
10. Johnson KC, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994-1997. *Cancer Causes and Control* 11: 211-221, 2000.
11. Lash TL, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* 149: 5-12, 1999. 12. Sandler DR, Everson RB Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 121: 37-48, 1985.
13. Jee SH, Ohrr H, Kim HS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *International J Epidemiol* 28: 824-828, 1999.
14. Lash TL, Aschengrau A. A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat* 75: 181-184, 2002.
15. Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao SY, Gim JSY, Ma HL, Butler J, Anton-Culver H. Breast cancer passive and active Cigarette smoking and N-acetyltransferase 2 genotype. *Pharmacogenetics* 10: 461-469, 2000.
16. Millikan RC, Pittman GS, Newman B, Tse CKJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA. Cigarette smoking, Nacetyltransferase 1 and 2 and breast cancer risk. *Cancer Epidemiology Biomarkers and Prevention* 7: 371-378, 1998.
17. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A. Active smoking household passive smoking and breast cancer: Evidence from the California Teachers study. *J Natl Cancer Inst* 96: 29-37, 2004
18. Wartenberg D, Calle EE, Thun MJ, Heath CW, Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* 92: 1666-1673, 2000.
19. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes and Control* 12: 797-802, 2001.
20. Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA. Active and passive smoking in breast cancer: Prospective results from the nurses' health study. *Epidemiology* 13: 138-145, 2002.
21. Wells AJ. Breast cancer, cigarette smoking and passive smoking. *Am J Epidemiol* 133: 208-210, 1991.

22. Wells AJ. Breast cancer, cigarette smoking and passive smoking. *Am J Epidemiol* 147: 991-992, 1998.

23. Press Release, IARC Monographs Programme declares secondhand smoke carcinogenic to humans. International Agency for Research on Cancer, 2002.